

FDA Media Call

Recommendation to remove Avastin indication for metastatic breast cancer

Moderator: Erica Jefferson

December 16, 2010

Coordinator: Welcome and thank you for standing by. At this time all participants are in listen only mode. After the presentation we'll conduct a question and answer session.

Today's conference is being recorded. If you have any objections you may disconnect at this time. And now I'd like to introduce your host for today's conference, Erica Jefferson.

You may begin.

Erica Jefferson: Thank you (Jeff). Good morning and thank you for participating in today's call. My name is Erica Jefferson and I'm from FDA's Office of Public Affairs.

This is a media briefing to announce FDA's recommendation to remove the breast cancer indication from the Avastin product label also known by it's chemical name, bevacizumab.

By now, FDA's press release for this announcement has posted to our Web site and will be distributed on the newswire.

Today I'm joined by Dr. Janet Woodcock, Director for the Center for Drugs. Dr. Richard Pazdur, Director for the Office of Oncology Drug Products, Dr.

Patricia Keegan, Director for the Division of Biologic Oncology Products and Denise Esposito, Deputy Director in the Office of Regulatory Policy within the Center for Drugs.

Dr. Woodcock will provide an overview of today's recommendation, Dr. Pazdur will briefly walk through the regulatory history of Avastin including FDA's 2008 decision to grant the drug an accelerated approval for metastatic breast cancer.

Dr. Keegan will take a few moments to review data from the four clinical studies that ultimately led to today's recommendation and Denise Esposito will briefly explain what a notice of opportunity for hearing is and what the proceedings involve.

After speaker remarks we will move to the question and answer portion of the call. Reporters will be in listen only mode until we open up the call for questions. When asking a question, please remember to state your name and affiliation.

Also, please limit yourself to one question and one follow-up so we can get to as many questions as possible.

Before we begin the briefing, I want to bring your attention to several materials that are now posted to FDA's Web site and can be accessed from a link in the news release.

An Avastin resource page has been created that contains a copy of the notice of opportunity for hearing letter sent to Genentech, Dr. Pazdur's decision memo on Avastin, an audio podcast featuring Dr. Woodcock and questions and answers.

We have also reposted the 2007 and 2010 FDA presentation to the oncologic drugs advisory committee on this page as well. With that, I will now turn it over to Dr. Woodcock for her opening remarks.

Dr. Woodcock?

Dr. Janet Woodcock: Thank you Erica.

Today we're here to announce that FDA has taken the first steps toward removing the breast cancer indication from the label of the cancer drug Avastin.

The drug's manufacturer, Genentech, has been notified in writing of FDA's decision and will now have 15 days to request a proceeding called a Notice of Opportunity for Hearing to dispute the agency's recommendation. That 15-day timetable is set by law and applies to drugs like Avastin that were approved under FDA's accelerated approval regulations for this indication.

If a hearing is requested and granted by FDA's commissioner, the company will have an opportunity to present additional information that might demonstrate Avastin's safety and effectiveness in breast cancer to an independent panel of experts selected by the Commissioner's office.

I want to state up front that FDA's ready to work with Genentech on any proposals to conduct additional studies of Avastin in patients with metastatic breast cancer designed to identify responsive tumors.

Today's announcement is the first step in a process and will not have an immediate impact on use of Avastin to treat breast cancer or the drugs availability.

For patients that means no disruption in treatment. Their access to Avastin will not be affected. Oncologists who are currently treating patients with Avastin in combination with chemotherapy for metastatic breast cancer should use medical judgment in deciding whether to continue treatment with the drug or explore other treatment options.

And I want to assure both patients and their doctors that Avastin's approval for metastatic, advanced colon, lung, kidney, and brain in other words glioblastoma, cancers, have in no way been affected by today's announcement.

Today's decision was a difficult one for the agency but certainly not unique. FDA's responsible for ensuring the products we approve for patients are both effective and safe.

What is considered safe may very depending on the severity of the disease being treated.

This is certainly true with cancer. Cancer drugs ordinarily have serious side effects that are related to their ability to kill or stop the growth of cancer cells. FDA understands that some serious risks from cancer drugs are acceptable to cancer patients as long as they're effective in prolonging life and improving quality of life.

While the FDA's willing to improve a relatively toxic cancer drug, we do so only if we believe the benefits to patients outweigh the severity of the drugs side effects.

FDA officials who have worked on this case have close personal experience with this disease. The team of medical reviewers evaluating Avastin are oncologists who have treated patients with breast cancer in academic or medical settings and also have been personally touched by the disease. The majority of these reviewers have been with FDA for more than a decade. Dr. Keegan, who's here today who heads the division reviewing this drug, oversaw the approval - a game changing breast cancer drug in 1998 that targeted her septum which targets the HER2 protein in metastatic breast cancer.

As for myself, I have personally reviewed the data with the team and support its recommendation because it is one that is based on the science and the evidence currently available to FDA.

FDA's recommendation to remove the breast cancer indication is based on the totality of the data available from four well-designed clinical studies called E2100, AVADO and RIBBON-1 which were for first-line or initial treatment of metastatic breast cancer and AVF2119g for second-line treatment of patients with metastatic breast cancer.

Each study was designed to evaluate or measure Avastin's safety and effectiveness in women with HER2-negative metastatic breast cancer.

After reviewing these data, FDA concluded that patients treated with Avastin did not live any longer than patients who were not treated with the drug. A

drugs ability to extend life is viewed by the FDA and many oncologists as the gold standard in assessing a cancer drug's effectiveness.

Although the drug did not extend life, patients on Avastin were at greater risk of experiencing severe side effects including side effects that are unique to Avastin such as development of perforations in places such as the nose, the stomach, the intestine. Many of these can be life threatening.

Other serious side effects such as severe high blood pressure, bleeding and hemorrhage, heart attack or heart failure, wound healing complications, organ damage or failure. And the development of a neurologic condition called reversible posterior leukoencephalopathy syndrome, or RPLS, characterized by high blood pressure, headaches, confusion, seizures, vision loss resulting from swelling of the brain have all been observed in patients treated with Avastin.

I also want to note that an independent advisory committee composed primarily of oncologists recommended by a vote of 12 to 1 let the agency remove the breast cancer indication from the Avastin label given the drugs a risk compared to its potential benefits.

Now, before I end, I want to emphasize that the FDA did not consider the cost of Avastin in making this decision. Reimbursement is a decision that's made by insurance providers who often use different criteria from those used by FDA when we determine that a drug is safe and effective for marketing.

At this time our sister agency, CMS, will not be making any changes to its reimbursement policy for Avastin and is waiting till the resolution of this process before deciding whether to make any changes.

The FDA's committed to working with Genentech on further research that might identify patients with metastatic breast cancer who have a high chance of responding to Avastin. If successful, such studies could allow FDA to approve an indication for the use of Avastin to treat breast cancer in a specific group of patients who have been identified as likely to respond to the treatment and we are certainly seeing more of this targeted therapy using diagnostic agents in drug development.

In closing, I'd like to thank the dozens of patients and their family members and friends who have personally reached out to me and other colleagues at FDA to share their personal experiences with the disease and with their treatment with Avastin and breast cancer.

We do not want to discount these treatment experiences and we wish those patients continued success.

With that, I will turn it over to Dr. Pazdur for some further discussion of the history of this indication.

Thank you.

Dr. Richard Pazdur: Thank you Dr. Woodcock. As mentioned, I will walk through the regulatory history of Avastin including the FDA's 2008 decision to grant the drug an accelerated approval for metastatic breast cancer.

Avastin in combination with intravenous 5 fluorouracil or 5-FU was first approved in February of 2004 to treat patients with first line metastatic colorectal cancer.

Since that time, the agency has granted approval for Avastin to treat non-small cell lung cancer in October 2006 and metastatic renal or kidney cancer in August of 2009.

In May of 2009, FDA granted accelerated approval for Avastin to treat glioblastoma. The agency is currently awaiting confirmatory studies for that indication. The drug was granted accelerated approval for the glioblastoma indication based on an overall response rate. That is, the percentage of patients in a clinical study who's cancer reduces in size or disappears on x-ray images.

The goal of the accelerated approval program is to provide earlier patient access to promising new drugs to treat serious or life-threatening diseases while confirmatory trials are conducted.

The program is also designed to allow for expedited withdrawal of drug where clinical benefit is not demonstrated by the confirmatory trials.

Genentech initially submitted a supplemental biologics application to FDA in May of 2006 seeking approval for Avastin in combination with paclitaxel chemotherapy. In the first line HER2-negative metastatic breast cancer population based on the results of the clinical study known as E2100.

In September of 2006, we issued a complete response letter requesting additional information regarding the E2100 study. This request included a request for an independent blinded review of patient scans for progression-free survival or PFS since the initial application included only investigator-assessed findings.

In August 2007, Genentech resubmitted the application and FDA announced a month later that we were taking the application to our Oncologic Drugs Advisory Committee or ODAC.

In December 2007, the committee recommended five to four against approval. However, in February of 2008, FDA approved Avastin in combination with Paclitaxel because the agency found, at that time, that it was appropriate to approve the drug for breast cancer under the agencies accelerated approval program.

This accelerated approval was based on the results from the study E2100. In that study, patients who received Avastin plus chemotherapy experienced a delay in the growth of their cancer. That is an improvement in progression-free survival or PFS.

This finding was based primarily on x-rays and CT scans. This delay was estimated to be over five months. This particular delay in tumor growth was considered by FDA to be an indirect measure of clinical benefit. If this delay was consistently seen across additional studies or an improvement in overall survival was noted, FDA would consider the findings in E2100 as a clinical benefit.

At the time, Genentech informed the FDA of several ongoing studies evaluating the effectiveness of Avastin in patients with metastatic breast cancer. In November of 2009, Genentech submitted the results of two studies, AVADO and RIBBON-1 which sought to confirm the results observed in E2100.

Unfortunately the magnitude of the delay in tumor growth observed in the E2100 trial was not evident in these two additional studies. In addition, a

study, AVF2119g which looked at the use of Avastin in the second or third line metastatic breast cancer population did not demonstrate a statistical improvement in PFS or overall survival.

In each of these three studies the delay of tumor growth was smaller than that which was observed in the E2100 trial. There was no significant improvement in overall survival. We, again, decided to seek the opinion of an outside group of experts on the Avastin data in breast cancer.

In July, ODAC recommended 12 to 1 that FDA remove the breast cancer indication from the Avastin's label. I understand that today's recommendation from the FDA is disappointing for patients with breast cancer. Please know that these findings are also disappointing for the FDA as well.

I oversaw the initial approval of Avastin for breast cancer in 2008 and hoped that the magnitude of improvement in PFS observed in the E2100 trial would be confirmed in additional clinical studies.

However, we have concluded that the benefits of Avastin in delaying progression of disease have not been shown to translate into prolonged survival of patients.

The additional trials identified to confirm the initial magnitude of improvement in PFS has also failed to accomplish this objective.

Given the number of serious and life threatening side effects, which Dr. Keegan will outline next, FDA does not believe that there is a favorable risk to benefit profile for the use of Avastin in the first line treatment setting of breast cancer.

The Office of Oncology Drug Products is committed to approving drugs that are effective for patients relative to their side effect profile. I want to reiterate that the approved indications for lung, kidney, colorectal and brain cancer or glioblastoma are not impacted by today's decision.

The breast cancer indication has not been removed yet and the drug will be available for patients. Oncologists should use their medical judgment when determining whether they should continue treating patients with this drug. A list of FDA approved breast cancer treatment options are posted on our Web site.

The Web site can be accessed through today's news release. As Dr. Woodcock noted, FDA is open to reviewing data from additional studies the company conducts that shows the benefits of Avastin outweigh the risk. If successful, such studies could allow FDA to approve an indication for the use of Avastin to treat metastatic breast cancer in a subpopulation of patients who have been identified.

I too want to thank patients and my colleagues in the oncology field for sharing their comments and concerns with me over the past several months. I want to thank the review team responsible for evaluating Avastin in breast cancer who have spent the last several years reviewing data from these studies that have led to today's recommendation.

With that I will turn it over to Dr. Keegan who will briefly outline the results of these studies.

Dr. Keegan?

Dr. Patricia Keegan: Thank you.

Good morning I'm Dr. Patricia Keegan from the Division of Biologic Oncology Products at FDA.

My remarks will cover the trial designs and the overview of the individual results of the clinical trials reviewed by FDA that led to today's action.

The basis for today's actions were four clinical trials conducted in patients with HER2 negative breast cancer enrolling more than 3000 women. The data from these trials is mature with regards to the reported affects on progression free and overall survival.

Three of these trials, E2100, AVADO and RIBBON-1 enrolled women with metastatic breast cancer who had not yet received chemotherapy for treatment of their metastatic disease.

These are the trials that FDA refers to as trials conducted for the first line treatment of metastatic breast cancer. A fourth trial, AVF2119g, was conducted in women who had received one or more prior chemotherapy regimens for metastatic disease.

This trial was included in FDA, the valuation of efficacy as it was the initial trial conducted by Genentech that was intended to support a marketing claim for Avastin in the treatment of metastatic breast cancer.

E2100 was sponsored by the National Cancer Institute and conducted by the Eastern Cooperative Oncology Group as part of the clinical research agreement or, (CRATA), between Genentech and the NCI.

Study E2100 was a multi-center randomized open label trial that enrolled 722 patients almost exclusively in the United States between January 2002 and May of 2004.

All patients received Paclitaxel at a dose of 90 milligrams per meter squared on days 1, 8 and 15 of the 28-day cycle. Patients were randomized to receive no additional therapy or (concomitant) Avastin at a dose of 10 milligrams per kilogram on days 1 and 15 of each cycle. Patients continued therapy until disease progression.

Patients were eligible for E2100 if they had locally recurrent or metastatic breast cancer and had not received prior chemotherapy for metastatic disease.

Patients with HER2-positive disease were excluded unless they had received previous necessary therapy with Herceptin. However, E2100 did not require patients to have measurable disease. The primary endpoint for this trial was progression-free survival. Secondary endpoints included objective response rate, overall survival, quality of life assessment by patient reported questionnaires and safety.

The trial was declared positive by an independent data monitoring committee at its first planned interim analysis after approximately 50% of the reported events that occurred.

The second trial I will describe is the AVF2119g. This was, again, an open label multi-center randomized trial, however, it was conducted in women receiving second or third-line treatment for metastatic breast cancer.

The trial enrolled 462 women who had previously received taxane and anthracycline for the treatment of breast cancer and patients were enrolled between November of 2000 and March of 2002.

All patients were required to have measurable disease. These patients received capecitabine at a standard dose and were randomized to received either no additional therapy or Avastin in combination with capecitabine at a dose of 15 milligrams per kilogram every three weeks.

The primary endpoint of this trial was also progression-free survival, however, it was based on the determination of an independent review committee as a prospective component of the trial. Secondary endpoints included overall survival, objective response rate, quality of life assessments by patient reported questionnaires and safety.

In September of 2002 the FDA was informed that the AVF2119g trial failed to meet its primary endpoint.

The third trial is the AVADO trial. This is a randomized double-blind international study conducted in women with metastatic or locally recurrent HER2-negative carcinoma of the breast who had not received prior chemotherapy.

All patients received a docetaxel at a dose of 100 milligrams per kilogram every three weeks and were randomized to one of three arms; a placebo, Avastin at a dose of 7.5 milligrams per kilogram or Avastin at a dose of 15 milligrams per kilogram.

The primary efficacy endpoint of this trial was investigator assess progression- free survival. The key secondary endpoints were overall response

rate and overall survival. In addition, quality of life was assessed by patient reported questionnaires.

The AVADO trial enrolled 735 patients between March 2006 and October 2007 at clinical study sites in Western Europe, Australia, Canada, Eastern Europe, Asia and Central and South America.

The RIBBON-1 trial is a randomized double-blind international study conducted in women with metastatic HER2-negative breast cancer who had not received prior therapy for metastatic disease.

Eligible patients received bevacizumab or placebo in combination with either an anthracycline, taxane or capecitabine.

Choice of chemotherapy was at the discretion of the investigator and was specified prior to randomization. The primary endpoint of this trial was investigator-assessed progression-free survival with key secondary endpoints of overall response rate and overall survival.

This trial was a parallel group design in which patients who received taxane's or anthracycline were analyzed together and patients who received capecitabine were analyzed as an individual cohort.

The study was adequately powered to assess progression-free survival in each chemotherapy cohort and enrolled 1237 patients, 622 in the anthracycline taxane cohort and 615 in the capecitabine cohort at clinical sites in the US, Europe and other parts of the world between December of 2005 and July 2008.

I will now briefly summarize the results. In the E2100 trial there was a statistically significant improvement in progression-free survival. This was determined by retrospective review of radiology studies and clinical information on case report forms conducted by an endpoint review panel, (NASTA) treatment assignment.

The median progression-free survival time was 11.3 months in the Avastin/paclitaxel arm and 5.8 months in the paclitaxel alone arm for a difference of 5.5 months.

There was a 52% reduction in the instantaneous risk of death or disease progression that's reflected in the hazard ratio of 0.48. There was, however, no significant difference in overall survival with median survival times of 24.8 months in the paclitaxel group and 26.5 months in the bevacizumab or Avastin plus paclitaxel group.

The tumor response rate was higher in the bevacizumab arm as compared to paclitaxel alone.

The AVADO trial (had) a statistically significant improvement in progression free survival for each of the two bevacizumab containing arms as compared to the placebo arm based on investigator-assessment of disease progression.

The median progression free survival time was 8.8 months in the Avastin 15 milligram per kilogram plus docetaxel arm as compared to 7.9 months in the docetaxel alone arm; a difference of 0.9 months.

The median progress free survival time was 8.7 months in the Avastin, 7.5 milligram per kilogram docetaxel arm and 7.9 months in the docetaxel alone arm; a difference of 0.8 month. It was a 30 and 38% reduction in the risk of

disease progression or death as reflected in the hazard ratios of 0.7 and 0.62 for the 7.5 milligram per kilogram Avastin arm and the 15 milligram per kilogram Avastin arm respectively as compared to placebo.

There was no survival benefit with the addition of Avastin to docetaxel at either Avastin dose level. Mature survival showed a hazard ratio of 1.103 favoring the placebo arm over the 7.5 milligram per kilogram Avastin arm.

Similarly, the hazard ratio for overall survival was 1.03, again, favoring the placebo arm over the 15 milligram per kilogram arm. Please note these are not significant differences.

The objective response rate was higher in the bevacizumab containing arms compared to placebo with objective response rates of 44% in the placebo arm, 55% in the Avastin 7.5 milligram per kilogram arm and 63% in the Avastin 15 milligram per kilogram arm.

In the taxane/anthracycline cohort of the RIBBON-1 study the addition of bevacizumab to anthracycline or taxane based chemotherapy demonstrated a statistically significant improvement in progression free survival as compared to chemotherapy alone.

The median progress free survival time was 9.2 months in the Avastin containing arm and eight months in the chemotherapy alone arm for a difference of 1.2 months.

This was - there was a 36% reduction in the risk of disease progression or death as reflected in the hazard ratio of 0.64. There was no survival benefit with the addition of Avastin to anthracycline or taxane based chemotherapy.

The mature survival analysis yielded a hazard ratio of 1.11 favoring the placebo arm.

There was a higher objective response rate in the bevacizumab containing arm with an absolute increase of 13.5% in the overall response rate with the addition of bevacizumab to anthracycline or taxane based chemotherapy.

In the capecitabine cohort of the RIBBON-1 trial the addition of the Avastin to capecitabine demonstrated a statistically significant improvement and progression-free survival.

A median progression-free survival time was 8.6 months in the Avastin/capecitabine arm and 5.7 months in the capecitabine alone arm for a difference of 2.9 months. There was a 31% reduction in the risk of disease progression or death as reflected in the hazard ratio of 0.69.

There was no survival benefit with the addition of bevacizumab to capecitabine. A comparison of mature survival data in the capecitabine cohort showed a hazard ratio of 0.88 favoring the bevacizumab containing arm.

To summarize, the three trials conducted in first line treatment with metastatic breast cancer, the magnitude of the difference in median progression-free survival between Avastin containing arms and the E2100 was 5.5 months. This size - the size of this treatment effect is not confirmed by the 0.9, 1.2 and 2.9 month differences in median progression-free survival seen in the AVADO and the taxane/capecitabine cohorts of the RIBBON-1 study.

In addition, none of these studies show that the addition of Avastin to standard effective chemotherapy resulted in better survival.

Similarly in the AVF2119g trial conducted in women receiving second or third line breast cancer, there was no evidence of an improvement in the overall survival.

In this trial there was also no difference in progression free survival. There was a slightly higher objective response rate, 19 versus 9%. However the duration of those responses were short, five months in medium duration in the Capecitabine plus Avastin arm 7-1/2 months in Capecitabine alone.

Quality of life questionnaires (as I said a) were used in three of the studies, AVF2119g, E2100 and AVADO. Due to the open label trial design and amount of missing data, both at baseline and after treatment, evaluation to be viewed with caution.

However, as reported by Genentech, there was no evidence of clinically important differences based on quality of life questionnaire results reported by patients in the Avastin containing arm as compared to the chemotherapy-containing arm.

FDA also reviewed the toxicity reported into the four trials. There were no new types of adverse events identified. There was an increase in incidents of hypertension, hemorrhage, impairment of wound healing, perforation, fistula formation, proteinuria and severe neutropenia.

There was a high proportion of patients who had treatment held or discontinued for toxicity. Within each study or cohort there was a consistent finding of a 14 to 20% increase in NCI common terminology criteria toxicities, those that are reported as severe or life threatening in the bevacizumab (ambient) containing arm as compared to the control arms.

Right. So I'm going to direct this back to Dr. Pazdur. Oh, I'm sorry, to Ms. Esposito at this point.

Denise Esposito: Thank you Dr. Keegan. As Dr. Woodcock mentioned at the outset in her opening remarks, today's action is not the withdrawal of the metastatic breast cancer indications from Avastin's label. It's the beginning of regulatory process.

And because the process for withdrawal of accelerated approval indications or drugs is different from the standard withdrawal process, I'm going to explain what the process looks like and give you an overview of how it'll play out.

Today as Dr. Woodcock mentioned, the agency has issued a letter to Genentech, the manufacturer, containing a notice of an opportunity to request a hearing. And that notice was placed in a public docket. And the Web page that was mentioned at the beginning of this call will have a link to that document. And the letter can be accessed there.

From the receipt of the letter today, Genentech will have 15 days to tell the agency whether it would like to request a hearing. If it does request a hearing, the manufacturer will have 30 days to submit a data package that includes all data and information that was part of the supplement package and on which they intend to rely at the hearing.

The hearing is not automatically granted. The agency goes through a process where it reviews the materials to determine whether a hearing is warranted. And what the agency requires to grant a hearing is that the - that Genentech establish in its submission that there are material facts in dispute that actually require a hearing to be resolved.

If the agency does grant a hearing, we will publish a Federal Register notice that announces the date and time of the hearing. The format of the hearing would be a public hearing under Part 15 of our regulations but as modified slightly by our accelerated approval regulations.

It's not a formal evidentiary hearing. It will be presided over by the Commissioner or her designee and there'll be an Advisory Committee present at the meeting. It's not a voting Advisory Committee.

The function of the Advisory Committee is to review all of the data and information that's presented, listen to the questions and issues that come up at the hearing, ask their own questions if they would like and then provide advice and recommendations to the Commissioner.

The process of the hearing is a question - a presentation and question and answer, sorry, structure. The presiding officer, the Advisory Committee members, members of the manufacturer's representative team and representatives of the Center for Drugs will be permitted to ask questions at the hearing. And the presiding officer may also take questions in his or her discretion from others present at the public hearing and ask them to the presenters at the hearing.

There will not be a decision made at the hearing. Following the hearing the Commissioner and the participants from the agency side on the hearing evaluate the outcome of the hearing and then will render a decision. That decision will be in writing. And that is the decision that constitutes the final agency action and would give the manufacture recourse if they choose to go that route.

I guess with that, I'll turn it back over to Erica.

Erica Jefferson: Thank you Ms. Esposito. At this time we will begin the question and answer portion of the briefing. I want to remind reporters to ask one question and one following. (Jeff), we'll take our first question.

Coordinator: If you would like to ask a question, please press star 1. To withdraw your question, please press star 2. Again, if you would like to ask a question, please press star 1. One moment please for the first question.

The first question is from Lisa Richwine. Your line is open.

Lisa Richwine: Hi. Thanks for taking my question. I just had a follow up question on the process that was just being described. For the hearing, is there an Advisory Committee there or any kind of outside experts? Would they be the same people that were on the Advisory Committee before? And will any outside experts make a recommendation as we usually see in an Advisory Committee? I understand that the final decision will be made there.

Denise Esposito: Is there - yes there will be an Advisory Committee present. It is not necessarily the same Advisory Committee. The regulations don't specify. So that Advisory Committee would be present at the hearing. They would ask questions. They are able to ask questions. They are able to ask follow up questions and they present a recommendation to the Commissioner and the presiding officer.

Erica Jefferson: Did that answer your question?

Lisa Richwine: Okay.

Erica Jefferson: That was Denise Esposito.

Lisa Richwine: Thank you. Can I just follow up? Would you exclude people who were previously on the committee because they would - it would seem like they already have an opinion?

Denise Esposito: I don't think that anybody would necessarily be excluded by prior service on the committee.

Lisa Richwine: Okay. Thanks.

Erica Jefferson: Next question (Jeff).

Coordinator: Next question is from Catherine Larkin. Your line is open.

Catherine Larkin: Hi. Thanks for taking the question. I wanted to follow up again on this process for a hearing. Is there any example from the past or does the agency have any guidance on how long this process might take as far as posting a notice on the Federal Register, scheduling a hearing and making an ultimate decision?

Denise Esposito: This is an unusual process. We have not done this in the recent past. As I mentioned during my remarks, Genentech will have 15 days to request a hearing and then up to 30 days to submit the package. The agency will then deliberate on whether to grant a hearing.

If the hearing is granted, we have to constitute an Advisory Committee and set up the hearing. So I can't comment on precisely how long that will take but it's not, you know, it won't be in the next 30 to 60 days.

Catherine Larkin: And just one question in follow up to that. Will the agency accept any public comment at that time in regards to whether to have a hearing and what - and as far as what the ultimate outcome of that hearing should be?

Denise Esposito: The docket that has been opened today that contains the notice of opportunity for a hearing is also set up to accept public comments. So any comments such as that could be submitted to the docket.

Catherine Larkin: Great. Thank you.

Erica Jefferson: That was Denise Esposito again. (Jeff), next question.

Coordinator: Next question is from Andy Pollack. Your line is open.

Andy Pollack: Yes. I apologize. I missed a little bit at the beginning. But the EMA apparently has decided to retain the approval for breast cancer based on, you know, I assume the exact same data. I was wondering if you could comment on why there's a difference in these decisions.

Dr. Richard Pazdur: This is Richard Pazdur. Let me start this and I'll ask my colleagues if they'd like to join in or offer any additional information on this. One has to take a look at the issue. Our approval of Avastin in breast cancer was an accelerated approval.

As you are aware, the EMEA - EMA has a similar program called conditional approval. This was not used in this situation. So their initial approval for the drug on the E2100 trial was a regular or full approval.

I'd like to remind you that the contingencies of our accelerated approval was for the demonstration of clinical benefit. It's the same magnitude - an

impressive magnitude of PFS or overall survival to be demonstrated in the AVADO trial and the RIBBON-1 trial.

This data has also been submitted to the EMA and they have not agreed to any labeling extension. Therefore supporting our viewpoint that this additional data in breast cancer does not convey clinical benefit.

Erica Jefferson: Thank you. Andy did you have a follow up?

Andy Pollack: Well just a slightly different subject. Genentech submitted additional information, which caused you to delay the decision by three months. Could you discuss at all what that data might have been? I'm not sure if there's confidentiality or not on that. And also what's the prospect for some sort of test to more closely tailor Avastin to the breast cancer patients who might benefit?

Dr. Janet Woodcock: This is Janet Woodcock. We can't discuss the particulars of what was submitted by Genentech and went into their extension of the time. However, we reviewed all the totality of the data in making the decision that we're - recommendation that we're putting forth today. So we took into account everything that has been submitted to us on this subject.

Of course we are very interested in targeted therapy. We don't doubt based on the data that this drug is an active drug. It has some activity in breast cancer. But it doesn't translate right now to prolonging survival. All right. And I don't think anyone is in disagreement over those facts.

We have four studies that show there's no survival benefit once this - when this drug is given to people with metastatic breast cancer. But there is some tumor response. We agree with that.

So the question is either - there are multiple scenarios here. Either there's a subgroup of people whose tumors are particularly responsive to the drug. And if those could be identified, potentially that would be a subgroup who could be treated. Or perhaps people - the tumors respond but the relapse is very fast and the resistance develops quickly and the tumors overcome the intervention.

So there are multiple scenarios. But right now it's not the targeted therapy. It was the indication recommends it more or less for all comers in combination with other chemotherapy regimens.

So we have reviewed all the data. This is - every scientific piece of scientific information that is available that has been submitted to us we have looked at.

And these are the conclusions we've come to. And we certainly hope that additional data could be generated if there is a responsive subset of tumors.

Erica Jefferson: Thank you Dr. Woodcock. (Jeff), can we take the next question please?

Coordinator: The next question is from Carolyn Belcher. Your line is open.

Carolyn Belcher: Yes. Thank you. I was wondering if there is any precedent for what will happen to people who were currently on the drug and their doctor's, you know, they believe it's working. You know, are they going to be - is indication for them going to be removed or might it be possible that for people who are on it currently it will be - it will retain even after this final decision comes in a couple months?

Dr. Richard Pazdur: Well all I could discuss is what we have at hand. And this is a process that has been set in motion here. The indication has not been removed. And we

would encourage at this time patients to discuss with their physicians what the appropriate course of action should be.

Erica Jefferson: Carolyn.

Carolyn Belcher: Okay.

Erica Jefferson: Did you have a follow up?

Carolyn Belcher: I suppose is there - what is the timeframe for these targeted therapy studies or other ongoing studies to figure out how to do more targeted therapy? And if so, are they anywhere near culminating or will that take much longer?

Denise Esposito: Those questions would have to be directed to the companies really in charge of developing the drug.

Carolyn Belcher: Okay.

Denise Esposito: But we are very open to this course of action.

Carolyn Belcher: Okay. Thank you.

Erica Jefferson: Thanks (Carolyn). (Jeff), can we have the next question please?

Coordinator: The next question is from Alicia Mundy. Your line is open.

Alicia Mundy: Hi. Thank you for taking my call. I'd like to direct my question to Dr. Pazdur. And I would like to ask if he could clarify or go over the issue with the EMA and them having the same data but sort of not agreeing or agreeing. Could you clarify that Dr. Pazdur?

Dr. Richard Pazdur: Okay. Well what I could say - and here again, I'm not privy to the exact EMEA decision-making discussions that occurred within that agency. And I would refer you basically to a discussion with those regulatory authorities.

What I can say is that our approval of Avastin was under our accelerated approval program. When looking at the initial application, obviously we had concern of the fact - by the fact that we had a large affect on PFS without a demonstrated survival advantage.

And in addition there were issues of missing data in the application as well as the fact that the analysis was an interim analysis, which terminated the trial, which sometimes leads - which sometimes leads to a random high event from occurring. And that's why we were very concerned about getting additional data in - based on scene if this five-month improvement in PFS could be replicated in other studies.

We did request the additional data from the AVADO trial and the RIBBON-1 trial to be submitted. That identical data was submitted also to the EMEA. It is my understanding from the EMEA that they are not going to do a labeling extension and granting additional labeling claims based on combining Avastin with Capecitabine nor are they going to continue their labeling claim of Avastin plus Docetaxel.

So their viewpoint on the trial - the AVADO trial and the RIBBON-1 trial, are consistent with our viewpoint that these additional trials do not convey clinical benefit.

Alicia Mundy: Okay.

Dr. Janet Woodcock: So in other words, this is Janet Woodcock. Where we differed is with EMA is that the original approval at that time when we approved this indication, we indicated in our - by giving accelerated approval that we felt this was only reasonably likely, not proven to be associated with clinical benefit. That's why we gave an accelerated approval.

And our accelerated approval then required that clinical benefit be shown by the subsequent trial. As Dr. Pazdur just said, we agree with EMA that clinical benefit was not shown by the subsequent trials. All right. So that leads to our conclusion that in the accelerated approval was not confirmed. All right.

However, the EMA who did not originally have an accelerated approval, it simply leaves the conclusion that these two trials did not confirm a positive benefit risk. So the difference in the direction is due to our original skepticism that the PFS demonstrated in the 2100 trial would correlate with clinical benefit.

Alicia Mundy: Okay. I got - thank you very much.

Erica Jefferson: (Jeff), next question please.

Coordinator: The next question is from Matt Perrone. Your line is open.

Matt Perrone: Hi guys. Thanks for taking our questions. I'm a little confused on the role or the importance of the survival end point here. It seems like everyone's talking about that. I thought the condition of approval was just that these follow up studies would confirm the original clinical benefit that 5-1/2 months.

Now you talked to the company. They say, you know, the survival benefit was never part of the condition of approval. Can you comment on that a little bit?

Dr. Richard Pazdur: Yeah. This is Dr. Pazdur. The conditions for the accelerated approval were to demonstrate a similar magnitude in improvement of progression free survival or an improvement in overall survival. So it was an or here.

Unfortunately none of the trials showed an improvement in overall survival. And the - each one - the AVADO trial and the RIBBON-1 trial failed to disclose the same magnitude of benefit on PFS that was demonstrated in the E2100 trial.

Matt Perrone: So if they had given that five-month progression pre-survival, we wouldn't be having this call. The drug would be approved.

Dr. Richard Pazdur: The drug is approved.

((Crosstalk))

Matt Perrone: ...we're talking about - indication would be.

Dr. Richard Pazdur: You are correct.

Matt Perrone: Okay. Great. Thanks.

Erica Jefferson: Thanks Matt. Thanks Matt. (Jeff) we have time for two more questions.

Coordinator: The next question is from Donna Young. Your line is open.

Donna Young: Thank you so much. I have a question going back again to what Ms. Esposito was saying about this type of hearing when she said that this is an unusual process and you haven't done it in the recent past.

As far as like is - will this - if they do move forward and you have the hearing and then the outcome is still that you plan to remove it from the labeling, will this still be the first time under an accelerated approval that this whole process will be done? Can you go back to that again because I was confused when she said in the recent past? Thank you.

Denise Esposito: Sure. Sure. This is not the first time that the agency has initiated the process of withdrawing an accelerated approval drug or indication. It is - if this hearing were to occur, and it depends on the timing because as you may know there are others in process. This - if the hearing goes forward, it will be the first time that a manufacturer did not agree to withdraw voluntarily and the hearing process played out in full under the accelerated approval statute and regulations.

Erica Jefferson: Donna, does that answer your question?

Donna Young: Yeah. And let's see. She did say that there was a previous one as far as like that have been with the accelerated approval.

Denise Esposito: There have been other notices of opportunity for a hearing issued on drugs that were approved through our accelerated approval program and those are in the public record.

Donna Young: Okay. And then as far as like the decision timing, again going back to when the FDA would actually put that in the Federal Register if they decide not to move forward with the hearing, what would the timing on that be if they decide not to move forward with the hearing?

Denise Esposito: As I mentioned earlier, we can't predict the timing at this point. But the process of Genentech's submissions will take us through the end of January and the agency will decide on its course thereafter.

Donna Young: Thank you so much.

Erica Jefferson: Thanks Donna.

Donna Young: Thank you.

Erica Jefferson: Thanks Donna. (Jeff), we'll take our last question please.

Coordinator: Next question is from Fran Lowry. Your line is open.

Fran Lowry: Thank you. Did any of those four studies point to a particular subgroup of patients that would benefit from Avastin?

Erica Jefferson: Dr. Keegan.

Dr. Patricia Keegan: There were a number of subgroup analyses that were explored in all the trials as is commonly done. And there was no subset that appeared to be different from the general trial results. There was - in terms of either patients not deriving PFS benefit or deriving a substantially greater benefit that was not explainable by, you know, small numbers and subgroup analyses.

So no, there was no evidence in routine exploratory analyses that there was a population that might benefit.

Erica Jefferson: Fran, does that answer your question?

Fran Lowry: Yes. Thank you.

Erica Jefferson: At this time Dr. Woodcock will make a closing remark.

Dr. Janet Woodcock: Well, thank you very much and thank all of you on the call for your patience in listening to this. It's a complicated both from a legal, a procedural and scientific perspective. I believe there's still some questions about the differences in the approval between the European authorities and where FDA is.

First of all, let me make it completely clear to everyone that as far as the analysis of survival, we have four trials. None of these trials showed the drug-prolonged life in people with metastatic breast cancer, all right, in combination with various chemotherapeutic regimens that have been shown to prolong life themselves.

The EMA's original approval for this indication based on the original trial that was done was a full approval, which means they accepted that magnitude of progression free survival as predicting a clinical benefit.

FDA as you just heard said if we saw such a - we said that magnitude of progression free survival could be associated with a clinical benefit but it would have to be of a substantial magnitude. All right.

What we have is we have trials - we have the first trial which actually did have a substantial improvement in progression free survival and did not - was not associated with any survival benefits.

But now we have several other trials where we see - where we had a much smaller increase in progression free survival. And as far as we can tell there

was no symptomatic benefit to any patient. There was severe side effects. And there was no effect on overall survival in any of those trials, all four of the trials.

So for our point of view and we think from the EMA to some extent, these subsequent trials did not show a benefit, okay. However, because we had done an accelerated approval and these were - trials were intended to confirm that progression free survival magnitude of benefit and did not, now we find that overall we're looking at the totality of the data in metastatic breast cancer and that's what we see.

We see no overall survival. We see no evidence of benefit to patients - symptomatic benefit to patients. And so we see that the benefit compared to the risk of this drug in this particular population is not positive.

So in contrast since Europeans gave a full approval to the first - based on the first trial, they are simply looking at the secondary trial - the further trials and saying that they do now show benefit in combination with the chemotherapy regimen used in that case.

So those are the differences. But I think - what I would hope people would take away from this, none of the four trials showed any survival benefit. They did not show that adding Avastin to a variety of chemotherapeutic regimens improved - prolong the life of women with metastatic breast cancer. And they had - but it added to the chemotherapy - added many serious side effects. And so that's sort of the bottom line.

So I hope that sums it up. In summary, for FDA the progression free survival in this setting is only reasonably likely to be correlated with benefit and only if it's of a certain magnitude. Whereas for the EMA in this case progression

free survival they felt was reasonably likely to be correlated with the clinical benefit and that is why they did the full approval.

So thank you all for listening. And I hope that clarifies that situation. In general, the EMA really agreed with our assessment of these subsequent trials.

Erica Jefferson: Thank you Dr. Woodcock. This concludes today's media briefing. A replay will be available in about an hour and will be available for 30 days. Please remember to check FDA's Avastin resource page for more information. Thank you for your participation today and have a safe holiday everyone.

Coordinator: This concludes today's conference call. You may now disconnect.

END